Metabolic Aspects of Care of Neonatal Hypoglycemia.

Petter Karlberg, Ragnar Olegård and Karl-Göran Sabel.

Department of Pediatrics I, Göteborg University, Sweden.

At birth the fetal supply from the mother of glucose and aminoacids suddenly ceases. There is a rapid mobilization of fat from the subcutaneus depots (1) mediated by noradrenalin release (2). Hepatic glycogen stores will satisfy the glucose homeostatic demands for only a few hours. The baby becomes dependent upon sufficient hepatic gluconeogenesis for glucose homeostasis.

I will now share with you some results from our laboratories suggesting, that an adequate fat catabolism is essential to keep an adequate glucose homeostasis in the early neonatal period.

Olegård and co-workers studied the intravascular lipolysis from injected fat emulsion. Small-for-gestational-age (SGA) babies had a delayed intravascular lipolysis from the infused triglycerides compared to appropriate-for-gestational-age (AGA) babies, and the defect lipolysis was correlated to the degree of intra-uterine growth retardation (3,4). In the SGA babies, the uptake from the blood of released FFA was equally impaired (4).

Sabel and co-workers in the same laboratory found low FFA levels correlating with low levels of blood glucose at four hours of life in SGA newborn babies.
Moreover, the low free fatty acid levels correlated to low blood concentrations of beta-hydroxybutyrate, indicating that the lipolysis from the endogenous fat stores and fatty acid oxidation is also impaired in these infants (5). Slow elimination of injected fat emulsion also correlated with low initial blood glucose levels in these infants.

In the hypoglycemic SGA infants there was an accumulation of lactate and alanine initially, and the elimination of injected alanine was slower in the hypoglycemic than in the normoglycemic infants. Alanine injection had no effect on blood glucose in hypoglycemic infants (6). It was possible, however, to correct the hypoglycemia in these babies by infusing fat emulsion as Intralipid (5,6). The increase of glucose levels was correlated to the increase in beta-hydroxybutyrate (5). Concomitantly, a decrease of the respiratory quoitant and an increase in the oxygen consumption indicated utilization of fat (7). Although intravascular lipolysis was impaired, enough fatty acids were released from the high fat load to influence glucose homeostasis. Simultaneously blood concentrations of lactate and alanine decreased to the levels of the normoglycemic babies (5).

0300-5577/82/0102-0014 $ 2.00

Thus, we have indications of a defect lipolysis correlating to hypoglycemia. The hypoglycemia could be eliminated by fat infusion alone but not by infusion of gluconeogenic substrates alone.

In the Rhesus monkey, Sherwood and co-workers in Toronto, like in the present study, found significant positive correlation between plasma levels of FFA and blood glucose. They also showed a correlation between the FFA level and the rate of C^{14}- lactate incorporation into glucose, but no correlation to hepatic content of gluconeogenic enzymes (8).

Girard and co-workers in Paris have made extensive experiments on glucose homeostasis in newborn rat pups (9). Newborn rat pups lack subcutaneous white fat and are unable to mobilize endogenous fatty acids. They become deeply hypoglycemic, if they are not immediately suckling the very fat-rich rat milk, which contains seventy per cent of its calories as fat and only eight per cent as carbohydrates. The hypoglycemia in fasting newborn rat pups could be completely corrected by infusion of MCT fat alone but could not be corrected by infusion of gluconeogenic substrates alone (glycerol, lactate, pyruvate, alanine, serine, glutamin). There was no impairment of gluconeogenic enzymes in the fasting hypoglycemic rats and there was also a normal hormonal homeostasis favouring gluconeogenesis with low insulin and high glucagon blood levels.

These experiments in humans and animals strongly suggest that a normal function of lipid metabolism and utilization is necessary to accomplish adequate gluconeogenesis immediately after birth, which is necessary to establish normal glucose homeostasis after birth. Studies on rat and chicken liver have shown that an active fatty acid oxidation in the liver stimulates gluconeogenesis by providing acetyl-CoA, the obligatory activator of pyruvate carboxylase, and by providing the reducing equivalent, NADH, necessary to promote the reversible reaction towards the direction of gluconeogenesis (10, 11).

Practical implications.

Newborn babies are immediately dependent on fat utilization for normal glucose homeostasis.
Prophylactically all babies should be fed early with a diet containing a high fat content.
Breast milk with its high fat content should be supplied early, whenever possible. This is urgently needed in SGA babies as a profylaxis against potentially harmful hypoglycemia in these babies.
If adequate fat amounts could not be supplied early by the oral route, parenteral fat supplementation by a fat emulsion should be instituted early after birth.

In the treatment of manifest symptomathic or asymptomathic hypogly-

cemia, infusion of an adequate dose of intravenous fat emulsion should follow the immediate treatment by hypertonic glucose injection, thereby stabilizing the glucose homeostasis. The daily dose of Intralipid to these SGA babies should not exceed 2 gram fat per kilo body weight the first three days of life and thereafter not exceed 3,5 gram per kilo body weight for at least the next ten days (12). Intralipid administration should be spread out evenly thoughout the 24 hours to avoid infusion of high boluses of fat partides in a short time, which might temporarily interfere with pulmonary oxygen exchange.

In all instaces where nutrition is supplemented by intravenous fat administration to newborn infants, some breastmilk administration is always desirable, whenever possible, because of its content of carnitine, which is lacking in intravenous nutrition. Adequate supplementation with fat soluble vitamines should be added to the Intralipid^{R} emulsion as Lipovit^{R} additive. Water soluble vitamines, electrolytes and trace eliments should be added to the glucose or amino acid solutions.

1. Olegård, R.: Essential fatty acids in the neonatal period. In metabolism of blood lipids in newborn infants. Thesis. Göteborgs University (Gotab, Göteborg 1974).

2. Karlberg, P., Moore, RE. & Oliver Jr, TK.: The Thermogenic Response of the Newborn Infant to Noradrenaline. Acta Paediatr Scand 51: 284-292, 1962.

3. Gustafson, A., Kjellmer, I., Olegård, R. & Victorin, L.: Nutrition in low-birth-weight infants. I. Intravenous injection of fat emulsion. Acta Paediatr Scand 61: 149-158, 1972.

4. Olegård, R., Gustafson, A., Kjellmer, I. & Victorin, L.: Nutrition in low-birth-weight infants. III. Lipolysis and free fatty acid elimination after intravenous administration of fat emulsion. Acta Paediatr Scand 64: 745-751, 1975.

5. Sabel, K-G., Olegård, R., Mellander, M. & Hildingsson, K.: Interrelation between fatty acid oxidation and control of gluconeogenic substrates in small-for-gestational-age (SGA) infants with hypoglycemia and with normoglycemia. Acta Paediatr Scand, in press.

6. Mellander, M., Sabel, K-G., Niklasson, A. & Olegård, R.: Concequtive injections of L-alanine and fat emulsion in 4-hour-old hypoglycemic and normoglycemic small-for-gestational-age (SGA) infants: Effects on plasma concentrations of lipid and carbohydrate metabolites. Pediatr Res, 14:1421, 1980 (abstract).

7. Sabel, K-G., Olegård, R., Hildingsson, K. & Karlberg, P.: Effects of injected lipid emulsion on oxygen consumption, RQ, triglyceride, free-fatty-acid and β-hydroxybutyrate levels in small-for-gestational-age (SGA) infants. Acta Paediatr Scand, in press.

8. Sherwwod, WG., Robinson, BH., Mayes, S., Freire, E., Oei, J. & DiBattista, D.: Factors affecting gluconeogenesis in the neonatal subhuman primate (Macaca mulatta). Biol Neonate, 37: 67-74, 1980.

9. Girard, JR., Pegorier, JP., Lecturque, A. & Ferre, P.: Glucose homeostasis in the newborn rat. In Physiological and Biochemical Basis for Perinatal Medicine. Samuel Z. Levine Conf., 1st Int Meeting, Paris 1979, pp. 90-96 (Kargen, Basel 1981).

10. Utter, MF. & Keech, DB.: Pyruvate carboxylase. I. Nature of the reaction. J Biol Chem, 238: 2603-2608, 1963.

11. Ferre, P., Pregorier, JP., Williamson, DH. & Girard, J.: Interactions in vivo between oxidation of neon-esterified fatty acids and gluconeogenesis in the newborn rat. Biochem J, 182: 593-598, 1979.

12. Gustafson, A., Kjellmer, I., Olegård, R. & Victorin, L.: Nutrition in low-birth-weight infants. II. Repeated intravenous injections of fat emulsion. Acta Paediatr Scand, 63:177-182, 1974.

Prof.Dr.P.Karlberg
Göteborg University
Östrasukhusset
Smörslottsgatan 1
S-416 85 Göteborg